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Patent Office
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Mumbai - 400 013

THE PATENTS ACT, 1970

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IT IS HEREBY CERTIFIED THAT, the annex is a true copy of
Application and Provisional Specification filed on 06/06/2003 in respect of Patent Application
No. 582/MUM/2003 of CADILA HEALTHCARE LIMITED, a company incorporated under
the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat,
India.

This certificate is issued under the powers vested in me under
Section 147(1) of the Patents Act, 1970.

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DOCUMENT**

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COMPLIANCE WITH RULE 17.1(a) OR (b)

.....Dated this 25th day of June 2004.


(R. BHATTACHARYA)

ASST. CONTROLLER OF PATENTS & DESIGNS.

BEST AVAILABLE COPY

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT

(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, **CADILA HEALTHCARE LIMITED**, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

'NOVEL ANTIINFECTIVE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM'

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that the true and first inventor for the said invention are ,

Braj Bhushan LOHRAY, Vidya Bhushan LOHRAY & Brijesh Kumar SRIVASTAVA, all Indian citizens, of **CADILA HEALTHCARE LIMITED**, Zydus towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: **NIL**

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;
SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
Patent and Trademark Attorneys
E 556, Greater Kailash II,
New Delhi - 110 048, India.
Phone: 91 11 628 5603, 628 6012, 628 6025
Fax: 91 11 628 6005
Email: sna@vsnl.com

582/MUM/2003
6/6/2003

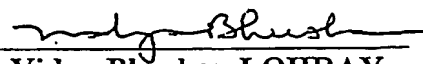
Received Rs. 2000	In Cash
Stamp No. 6/6/03	
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Registry of Valuation	
Date 6-6-03	80811

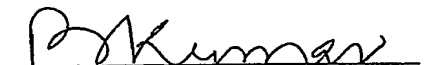
(7) Following declaration was given by the inventors

We, Braj Bhushan LOHRAY, Vidya Bhushan LOHRAY & Brijesh Kumar SRIVASTAVA, all Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

and the true and first inventors for this invention declare that the applicants herein is our assignees.


Braja Bhushan LOHRAY


Vidya Bhushan LOHRAY


Brijesh Kumar SRIVASTAVA

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

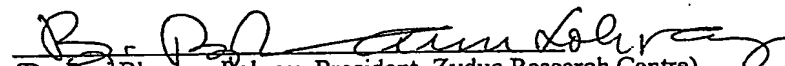
(9) Following are the attachments with this application:

- (a) Complete specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Power of Authority
- (d) Form 2 in triplicate
- (e) Power of Authority
- (f) Abstract

Fee Rs. in Cash/Cheque/Bank Draft Bearing No..... dated.....onBank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 5th day of JUNE, 2003.


(Dr. Braj Bhushan Lohray, President, Zydus Research Centre)
for CADILA HEALTHCARE LIMITED

To
The Controller of Patents
The Patent Office, at Mumbai

FORM 2

The PATENT ACT, 1970
(39 of 1970)
Provisional Specification

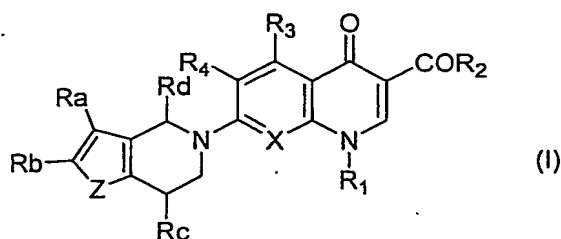
**NOVEL ANTIINFECTIVE COMPOUNDS, PROCESS
FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM**

CADILA HEALTH CARE LTD, Zydus Research Centre
Zydus Tower, Satellite Cross Road, Sarkhej-Gandhinagar Highway,
Ahmedabad-380015, Gujarat, India

The following specification describes the nature of the invention and the manner in which it is to be performed:

Field of Invention

The present invention relates to novel compounds of general formula (I), their analogs, their derivatives, their stereoisomers, tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts and pharmaceutical compositions containing them. The present invention also relates to a process of preparing compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, and novel intermediates involved in their synthesis.



Background to the invention

Antibiotic resistance is a serious concern worldwide as it would result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention though being primarily effective against Gram-positive pathogens are also effective against certain Gram-negative pathogens.

Gram-positive pathogens; for example Staphylococci, Enterococci, Streptococci and Mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*, community acquired pathogens (CAP), and so on.

Quinolones as a class of antibacterial agents are well known and are being used extensively throughout the world. They are potent inhibitors of gram positive as well as

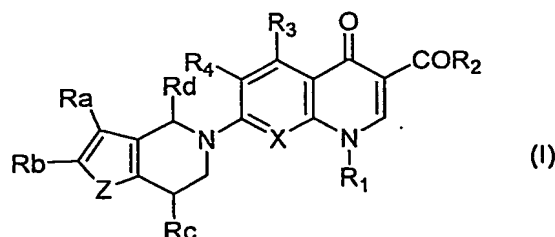
gram negative pathogens and may be administered orally or intravenously. A wide range of quinolone antibacterials have been introduced in the last decade which includes norfloxacin, ciprofloxacin, ofloxacin, and the recently launched gatifloxacin and moxifloxacin. However, some of the quinolone antibacterials have been associated with significant side effects (*J. Antimicrob. Chemother.*, 1994; 33: 685) and some of them have been discontinued at different stages of development (e.g. Trovafloxacin).

The quinolones inhibit bacterial growth by inhibition of DNA gyrase and topoisomerase IV (Gootz, *Medicinal Research*, 1996; Rev. 16:433). The gyrase interaction appears to rely on the N-carbonyl-carboxyl relationship at the C-7 position in the quinoline nucleus in this class of compounds. Quinolone antibacterials and their methods of preparation has been described in WO 0296908, WO 0153273, WO 0132655, WO 0129035, WO 9640190, WO 9640156, WO 9602540, US 4994599, US 4990517, US 4980470, US 4980373, US 4945160, US 4954507, US 4880814, US 4795751, US 4670444, OS 3816119, EP 0805156, EP 0421668, EP 0449445, EP 0300311, EP 0241206, EP 0235762, EP 0167763, EP 0155006, EP 0140116, EP 0028698, DE 3441788, DE 3519286, which are incorporated herein as reference in their entirety.

However, due to increase in antibacterial resistance and also otherwise there is a continuing need for discovering compounds which are more effective against resistant bacteria, have improved intestinal absorption, metabolic stability, and exhibit less toxicity.

Summary of the invention

The present invention describes a group of novel compounds useful as antibacterial agents. The novel compounds are defined by the general formula (I) below:

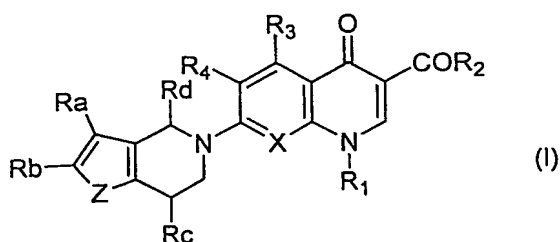


The compounds of the present invention are useful in the treatment of the human or animal body, as preventives and therapeutics agents for infectious diseases. The

compounds of this invention have excellent antimicrobial action against various human and veterinary pathogens including but not limited to multiply-resistant staphylococci and streptococci, as well as anaerobic organisms including those of the bacteroides and clostridia species, and acid-fast *Mycobacterium tuberculosis* and *Mycobacterium avium* with better efficacy, potency and minimum toxic effects.

Objectives :

The main objective of the present invention thus is to provide novel compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures suitable in the treatment of infectious diseases.



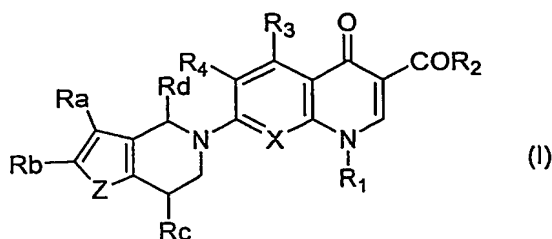
Another objective of the present invention is to provide a process for the preparation of novel compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, novel intermediates involved in their synthesis pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

Yet another objective of the present invention is to provide pharmaceutical compositions containing compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, their pharmaceutically acceptable salts, solvates and their mixtures having pharmaceutically acceptable carriers, solvents, diluents, excipients and other media normally employed in their manufacture.

Still another objective of the present invention is to provide a method of treatment of antibiotic resistant pathogens, by administering a therapeutically effective & non-toxic amount of the compound of formula (I) or their pharmaceutically acceptable compositions to the mammals.

Detailed Description of the description

The novel compounds of the present invention are defined by the general formula (I) below:



Wherein

R_1 represents hydrogen, linear or branched, substituted or unsubstituted groups selected from C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_{12} cycloalkyl; substituted or unsubstituted groups selected from aryl, heteroaryl or heterocyclic groups;

R_2 is selected from hydrogen, $-OBF_2$, $-BF_2$ or $-OR_6$,

Where R_6 represents hydrogen, C_1 - C_6 alkyl, C_3 - C_6 alkenyl or C_3 - C_6 alkynyl groups, which may optionally be substituted;

R_3 represents H, OH, linear or branched, substituted or unsubstituted groups selected from $-O(C_1-C_{12})$ alkyl, $-O(C_2-C_{12})$ alkenyl, $-O(C_2-C_{12})$ alkynyl, halo, NO_2 , CN, or $NR'R''$ groups, where $R'R''$ may be same or different and independently represent H, linear or branched, substituted or unsubstituted groups selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl or acyl groups;

R_4 represents H or halogen atom;

X represents N or $C-R_7$,

where R_7 represents H, $-OH$, $-(O)_n(C_1-C_6)$ substituted or unsubstituted alkyl where n is 0 or 1, $-NO_2$, $-NH_2$, $-NHCOCH_3$, $-CN$, $-COOH$ groups;

R_1 and R_7 can be taken together with the atoms to which they are attached to form a cyclic ring, which may optionally be substituted and may also optionally contain from 1 to 3 heteroatoms selected from O, N and S.

R_a , R_b may be same or different and represents hydrogen, halogen, haloalkyl, perhaloalkyl, haloalkoxy, perhaloalkoxy, hydroxy, thio, amino, nitro, cyano, formyl,

amidino, guanidino, or substituted or unsubstituted groups selected from linear or branched (C₁-C₁₂)alkyl, linear or branched (C₁-C₁₂)alkenyl, linear or branched (C₁-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, (C₁-C₁₂)alkenoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, ar(C₁-C₁₂)alkoxy, heterocyclyl, heteroaryl, heterocyclyl(C₁-C₁₂)alkyl, heteroar(C₁-C₁₂)alkyl, heteroaryloxy, heteroar(C₁-C₁₂)alkoxy, heterocycloxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, mono-substituted or di-substituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, hydroxyalkyl, aminoalkyl, mono-substituted or di-substituted aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, (C₁-C₁₂)alkylthio, thio(C₁-C₁₂)alkyl, arylthio, (C₁-C₁₂)alkoxycarbonylamino, aryloxcarbonylamino, aralkyloxcarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, alkyl hydrazino, alkoxyamino, hydroxylamino, derivatives of sulfenyl and sulfonyl groups, sulfonic acid and its derivatives, phosphonic acid and its derivatives;

R_c & R_d may be same or different and represents hydrogen, substituted or unsubstituted groups selected from alkyl, alkenyl groups;

Z represents O, S, N which may optionally be substituted;

The term "substituted" used in combination with other radicals, denotes suitable substituents on that radical such as substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted aryl, etc, mentioned anywhere in the specification. The suitable substituents include, but are not limited to the following radicals, alone or in combination with other radicals, such as, hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocycloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkoxycarbonylamino, aryloxcarbonylamino, aralkyloxcarbonylamino,

aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives.

The term "alkyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, *iso*-hexyl, heptyl, octyl and the like.

The term "alkenyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons; such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branched chains.

The term "alkynyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons, such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, and the like. The term "alkynyl" includes di- and tri-ynes.

The term "cycloalkyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term "cycloalkenyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, and the like.

The term "alkoxy" used herein, either alone or in combination with other radicals, denotes a radical alkyl, as defined above, attached directly to an oxygen atom, such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like.

The term "alkenoxy" used herein, either alone or in combination with other radicals, denotes an alkenyl radical, as defined above, attached to an oxygen atom, such as vinyloxy, allyloxy, butenoxy, pentenoxy, hexenoxy, and the like.

The term "cycloalkoxy" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like.

The term "halo" or "halogen" used herein, either alone or in combination with other radicals, such as "haloalkyl", "perhaloalkyl" etc refers to a fluoro, chloro, bromo or iodo group. The term "haloalkyl" denotes a radical alkyl, as defined above, substituted with one or more halogens; such as perhaloalkyl, more preferably, perfluoro(C₁-C₆)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups. The term "haloalkoxy" denotes a haloalkyl, as defined above, directly attached to an oxygen atom, such as fluoromethoxy, chloromethoxy, fluoroethoxy chloroethoxy groups, and the like. The term "perhaloalkoxy" denotes a perhaloalkyl radical, as defined above, directly attached to an oxygen atom, trifluoromethoxy, trifluoroethoxy, and the like.

The term "aryl" or "aromatic" used herein, either alone or in combination with other radicals, denotes an aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused, such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like. The term "aralkyl" denotes an alkyl group, as defined above, attached to an aryl, such as benzyl, phenethyl, naphthylmethyl, and the like. The term "aryloxy" denotes an aryl radical, as defined above, attached to an alkoxy group, such as phenoxy, naphthyloxy and the like, which may be substituted. The term "aralkoxy" denotes an arylalkyl moiety, as defined above, such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy, and the like, which may be substituted.

The term "heterocyclyl" or "heterocyclic" used herein, either alone or in combination with other radicals, denotes saturated, partially saturated and unsaturated ring-shaped radicals, the heteroatoms selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl,

piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, and the like; examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, and the like.

The term "heteroaryl" or "heteroaromatic" used herein, either alone or in combination with other radicals, denotes unsaturated 5 to 6 membered heterocyclic radicals containing one or more hetero atoms selected from O, N or S, attached to an aryl group, such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl, benzothienyl, indolinyl, indolyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, pyrimidonyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzoxazolyl, benzothizaolyl, benzimidazolyl, and the like.

The term "heterocyclalkyl" used herein, either alone or in combination with other radicals, represents a heterocycl group, as defined above, substituted with an alkyl group of one to twelve carbons, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl, and the like, which may be substituted. The term "heteroaralkyl" used herein, either alone or in combination with other radicals, denotes a heteroaryl group, as defined above, attached to a straight or branched saturated carbon chain containing 1 to 6 carbons, such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like. The terms "heteroaryloxy", "heteroaralkoxy", "heterocycloxy", "heterocylalkoxy" denotes heteroaryl, heteroarylalkyl, heterocycl, heterocyclalkyl groups respectively, as defined above, attached to an oxygen atom.

The term "acyl" used herein, either alone or in combination with other radicals, denotes a radical containing one to eight carbons such as formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, which may be substituted.

The term "acyloxy" used herein, either alone or in combination with other radicals, denotes a radical acyl, as defined above, directly attached to an oxygen atom, such as acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like.

The term "acylamino" used herein, either alone or in combination with other radicals, denotes an acyl group as defined earlier, may be CH_3CONH , $\text{C}_2\text{H}_5\text{CONH}$, $\text{C}_3\text{H}_7\text{CONH}$, $\text{C}_4\text{H}_9\text{CONH}$, $\text{C}_6\text{H}_5\text{CONH}$ and the like, which may be substituted.

The term "mono-substituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with one group selected from (C_1 - C_6)alkyl, substituted alkyl, aryl, substituted aryl or arylalkyl groups. Examples of monoalkylamino group include methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and the like.

The term "disubstituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with two radicals that may be same or different selected from (C_1 - C_6)alkyl, substituted alkyl, aryl, substituted aryl, or arylalkyl groups, such as dimethylamino, methylethylamino, diethylamino, phenylmethyl amino and the like.

The term "arylamino" used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through amino having a free valence bond from the nitrogen atom, such as phenylamino, naphthylamino, N-methyl anilino and the like.

The term "aralkylamino" used herein, either alone or in combination with other radicals, denotes an arylalkyl group as defined above linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-(1-naphthyl)ethylamino and the like.

The term "oxo" or "carbonyl" used herein, either alone ($-\text{C}=\text{O}-$) or in combination with other radicals, such as "alkylcarbonyl", denotes a carbonyl radical ($-\text{C}=\text{O}-$) substituted with an alkyl radical such as acyl or alkanoyl, as described above.

The term "carboxylic acid" used herein, alone or in combination with other radicals, denotes a $-\text{COOH}$ group, and includes derivatives of carboxylic acid such as esters and amides. The term "ester" used herein, alone or in combination with other radicals, denotes $-\text{COO}-$ group, and includes carboxylic acid derivatives, where the ester moieties are alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, naphthyloxycarbonyl, and the like, which may be substituted; aralkoxycarbonyl group such as benzyloxycarbonyl,

phenethyloxycarbonyl, naphthylmethoxycarbonyl, and the like, which may be substituted; heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group, is as defined above, which may be substituted; heterocyclyloxycarbonyl, where the heterocyclic group, as defined earlier, which may be substituted.

The term "amide" used herein, alone or in combination with other radicals, represents an aminocarbonyl radical ($\text{H}_2\text{N}-\text{C}=\text{O}-$), wherein the amino group is mono- or di-substituted or unsubstituted, such as methylamide, dimethylamide, ethylamide, diethylamide, and the like. The term "aminocarbonyl" used herein, either alone or in combination with other radicals, with other terms such as 'aminocarbonylalkyl', "n-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl", and "N-alkyl-N-hydroxyaminocarbonylalkyl", substituted or unsubstituted. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denotes aminocarbonyl radicals, as defined above, which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl, and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals.

The term "hydroxyalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

The term "aminoalkyl" used herein, alone or in combination with other radicals, denotes an amino ($-\text{NH}_2$) moiety attached to an alkyl radical, as defined above, which may be substituted, such as mono- and di-substituted aminoalkyl. The term "alkylamino" used herein, alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached to an amino group, which may be substituted, such as mono- and di-substituted alkylamino.

The term "alkoxyalkyl" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an alkyl group, such as methoxymethyl,

ethoxymethyl, methoxyethyl, ethoxyethyl and the like. The term "aryloxyalkyl" used herein, alone or in combination with other radicals, includes phenoxymethyl, naphthyloxymethyl, and the like. The term "aralkoxyalkyl" used herein, alone or in combination with other radicals, includes $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$, and the like.

The term "alkylthio" used herein, either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group of one to twelve carbon atoms, as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, such as methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like, which may be substituted.

The term "thioalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula $-SR'$, where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be substituted.

The term "arylthio" used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through a divalent sulfur atom, having a free valence bond from the sulfur atom such as phenylthio, naphthylthio and the like.

The term "alkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an alkoxycarbonyl group, as defined above, attached to an amino group, such as methoxycarbonylamino, ethoxycarbonylamino, and the like. The term "aryloxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aryloxycarbonyl group, as defined above, attached to the an amino group, such as C_6H_5OCONH , $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4(CH_3O)CONH$, $C_6H_4(OCH_3)OCONH$, and the like. The term "aralkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aralkoxycarbonyl group, as defined above, attached to an amino group $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2CH_2OCONH$, $C_6H_5CH_2OCONHCH_3$, $C_6H_5CH_2OCONC_2H_5$, $C_6H_4(CH_3)CH_2OCONH$, $C_6H_4(OCH_3)CH_2OCONH$, and the like.

The term "aminocarbonylamino", "alkylaminocarbonylamino", "dialkylaminocarbonylamino" used herein, alone or in combination with other radicals, denotes a carbonylamino ($-\text{CONH}_2$) group, attached to amino(NH_2), alkylamino group or dialkylamino group respectively, where alkyl group is as defined above.

The term "amidino" used herein, either alone or in combination with other radicals, denotes a $-\text{C}(=\text{NH})-\text{NH}_2$ radical. The term "alkylamidino" denotes an alkyl radical, as discussed above, attached to an amidino group.

The term "guanidino" used herein, either alone or in combination with other radicals, denotes $\text{HN}=\text{C}(\text{NH}_2)\text{NH}-$, suitably substituted with other radicals, such as alkylguanidino, dialkylguanidino, where the alkyl group, as defined above is attached to a guanidino group, such as methylguanidino, ethylguanidino, dimethylguanidino, and the like.

The term "hydrazino" used herein, either alone or in combination with other radicals, denotes $-\text{NHNH}-$, suitably substituted with other radicals, such as alkyl hydrazino, where an alkyl group, as defined above is attached to a hydrazino group.

The term "alkoxyamino" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an amino group. The term "hydroxyamino" used herein, alone or in combination with other radicals, denotes $-\text{NHOH}$ moiety, and may be substituted.

The term "sulfenyl" or "sulfenyl and its derivatives" used herein, alone or in combination with other radicals, denotes a bivalent group, $-\text{SO}-$ or RSO , where R is substituted or unsubstituted alkyl, aryl, heteroaryl, heterocyclyl, and the like.

The term "sulfonyl" or "sulfones and its derivatives" used herein, either alone or in combination with other radicals, with other terms such as alkylsulfonyl, denotes divalent radical $-\text{SO}_2-$, or RSO_2- , where R is substituted or unsubstituted groups selected from alkyl, aryl, heteroaryl, heterocyclyl, and the like. "Alkylsulfonyl" denotes alkyl radicals, as defined above, attached to a sulfonyl radical, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like. The term "arylsulfonyl" used herein, either alone or in combination with other radicals, denotes aryl radicals, as defined above, attached to a sulfonyl radical, such as phenylsulfonyl and the like.

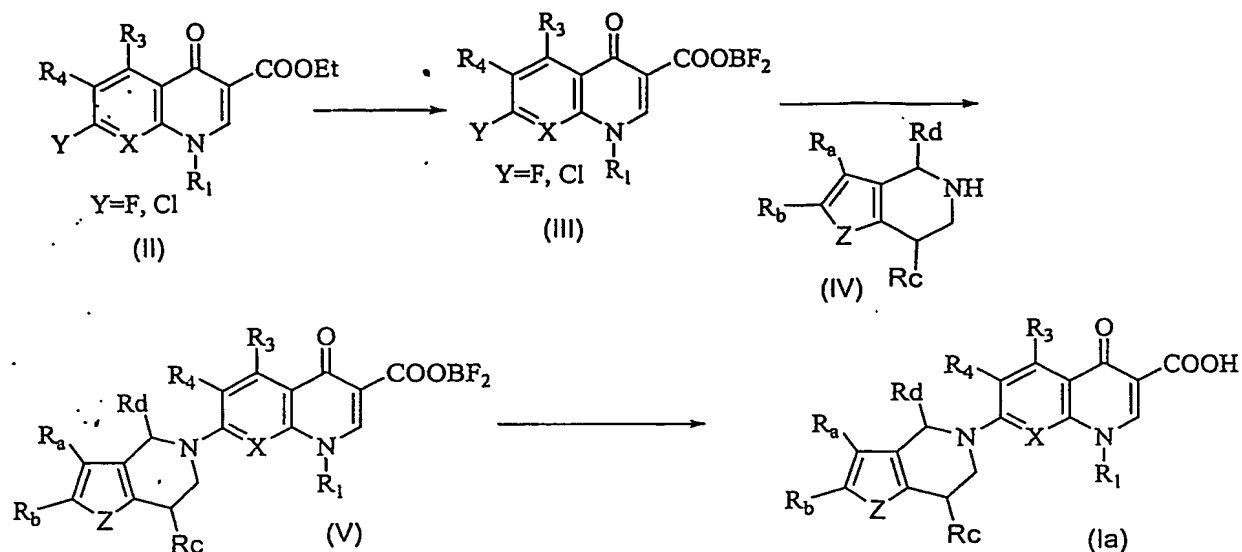
The term "sulfonic acid or its derivatives", used herein, either alone or in combination with other radicals, denotes $\text{-SO}_3\text{H}$ group and its derivatives such as sulfonylamino(SO_2NH_2); N-alkylaminosulfonyl and N,N-dialkylaminosulfonyl radicals where the sulfonylamino group is substituted with one and two alkyl groups respectively, such as N-methylaminosulfonyl, N-ethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl and the like; N-arylamino sulfonyl and N-alkyl-N-arylamino sulfonyl groups where the sulfonylamino group is substituted with one aryl radical, or one alkyl and one aryl radical; $\text{-SO}_3\text{R}$, wherein 'R' represents alkyl, aryl, aralkyl groups, as defined above, which may be substituted.

The term "phosphonic acid or its derivatives", used herein, either alone or in combination with other radicals, denotes P(O)(OH)_2 , $\text{P(O)(O(C}_1\text{-C}_6\text{ alkyl))}_2$, P(O)(O aryl)_2 , $\text{P(O)(OH)(O(C}_1\text{-C}_6\text{ alkyl))}$, and the like.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Several synthetic routes can be employed to prepare the compounds of the present invention well known to one skilled in the art of organic synthesis. The compounds of formula (I) can be synthesized using the methods described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art. Referred methods include, but not limited to those described below.

Scheme



Where $R_a, R_b, R_c, R_d, R_1, R_3$ & R_4 are substituents as described elsewhere in the specification and $R_2 = H$.

Compound of general formula (II) can be converted to their corresponding fluoborate ester of formula (III) through *trans* esterification using fluoboric acid at a temperature ranging from 40 °C to 100 °C. The compound of formula (III) is reacted with compound of general formula (IV) to give compound of general formula (V), using suitable organic bases such as triethylamine, N-N-diisopropyl ethyl amine and the like in solvents such as DMF, DMSO, pyridine, acetonitrile and the like or their mixture thereof, at a temperature ranging from 15 °C to 80 °C. Compound of formula (V) represents compounds of formula (I) where all symbols are as defined earlier and $R_2 = -OBF_2$. The fluoborate ester of formula (V) can be hydrolyzed to give compound of formula (Ia). Compound (Ia) represents compound of formula (I) where all symbols are as defined earlier and $R_2 = OH$. Suitable hydrolyzing agent may be selected from alcoholic KOH or NaOH and heating at 60-80 °C or using organic bases such as triethylamine, pyridine, piperidine and the like or their mixture thereof in 80-100% ethanol-water at reflux temperature. The compounds of formula (Ia) may be optionally converted to their corresponding esters, amides, acid salts by processes known in the art.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium *tert*-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride, magnesium alkoxide and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, *t*-butanol, 2-butanone, dioxane, propanol, butanol, isopropanol, diisopropyl ether, *tert*-butyl ether or mixtures thereof may be used. Organic bases such as lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, malic acid, lactic acid, maleic acid, salicylic acid, citric acid, ascorbic acid, benzene sulfonic acid, *p*-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, THF, acetonitrile, DMF or a lower alkyl ketone such as acetone, or mixtures thereof.

These salts may be in hydrated form- some of the compounds of the invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts".

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. T. W. Greene and P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Inc, 1999, 3rd Ed., 201-245 along with references therein gives such conventional methods and are incorporated herein as references.

It will be appreciated that the above-mentioned preparation of the compounds of Formula (I), or a pharmaceutically acceptable salts thereof, and/or pharmaceutically acceptable solvates thereof is a stereoselective procedure and that the compound of formula (I) is a single stereoisomer. Favorably, a compound of formula (I) is present in

admixture with less than 50% w/w of its racemic isomer, suitably 80 - 100 % and preferably 90 - 100 % pure, such as 90 - 95 %, most preferably 95 - 100 %, for example 95 %, 96 %, 97 %, 98 %, 99 %, and 99.99 % optically pure.

Because carbon-carbon double bonds also exist in the compounds, the invention contemplates various geometric isomers and mixtures thereof resulting from the arrangement of substituents around these carbon-carbon double bonds. These substituents are designated as being in the E or Z configuration wherein the term "E" refers to higher order substituents on opposite sides of the carbon-carbon double bond, and the term "Z" refers to higher order substituents on the same side of the carbon-carbon double bond. A thorough discussion of E and Z isomerism is provided in "Advanced Organic Chemistry. Reaction, Mechanisms, and Structure", 4th ed., John Wiley & Sons, New York, 1992, pp. 109-112, which is also incorporated herein as references.

Preferably the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or pharmaceutically acceptable solvate thereof is in optically pure form.

The absolute stereochemistry of the compounds may be determined using conventional methods, such as X-ray crystallography.

Another aspect of the present invention comprises a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their prodrugs, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates as an active ingredient, together with pharmaceutically employed carriers diluents and the like.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: the Science and Practice of Pharmacy, 19th Ed., 1995. The compositions may be in the conventional forms, such as capsules, tablets, powders, solutions, suspensions, syrups, aerosols or topical applications. They may contain suitable solid or liquid carriers or in suitable sterile media to form injectable solutions or suspensions. The compositions may contain 0.5 to 20 %; preferably 0.5 to 10 % by weight of the active compound, the remaining being pharmaceutically acceptable carriers, excipients, diluents, solvents and the like.

The compounds of Formula I are useful in the treatment of microbial infections in humans and other warm blooded animals, by either oral, topical or parenteral administration.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals including mammals, rodents, and the like. More preferred animals include horses, dogs and cats.

For the treatment of any of the above-mentioned diseases the compounds of formula (I) may be administered, for example, orally, topically, parenterally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula I according to this invention.

The quantity of active component, that is, the compounds of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating bacterial infections in humans and animals that have been diagnosed with having bacterial infections, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially active. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100 mg/kg, more preferably about 0.5 to about 100mg/kg of body weight/day. However, it should be appreciated that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection, and the particular compound being used. Also, it must be understood that the initial dosage administered may be increased beyond the upper level in order to rapidly achieve the desired blood level or the initial dosage may be smaller than the optimum and the and the daily dosage may be progressively increased during the course of treatment

depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g. two to four times per day.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes as previously indicated, in single or multiple doses. More specifically, the novel compounds described in the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. The carriers may include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents etc. Moreover, for oral consumption, the pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds as described in the invention are present in the compositions at concentration levels ranging from 5% to 60% by weight, preferably 10% to 50% by weight.

For oral administration, the tablets may be combined with various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine along with various disintegrants such as starch more preferably corn, potato or tapioca starch, alginic acid, sodium carbonate and certain complex silicates; together with binders like polyvinylpyrrolidone, sucrose, gelatin and acacia, humectants such as for example, glycerol; solution retarding agents, such as, for example paraffin; absorption accelerators such as, for example, quaternary ammonium compounds; wetting agents like cetyl alcohol and glycerol monostearate; absorbents like kaolin and bentonite clay. Additionally, magnesium stearate, sodium lauryl sulfate, talc, calcium stearate, solid polyethylene glycols and mixtures thereof are often added as lubricating agents for tableting purposes. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Similar type of solid compositions may also be employed as fillers and excipients in soft and hard gelatine capsules; preferred materials includes lactose, milk sugar or high molecular weight polyethylene glycols.

The active compounds can also be in micro-encapsulated form using one or more of the excipients noted above. The solid dosage forms of tablets, dragees, capsules, pills, and the granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings which are well known in the field of pharmaceutical formulation art. In such solid dosage forms the active compound may be admixed with atleast one inert diluent such as sucrose, lactose and starch. They may also contain, additional substances for e.g. tableting lubricants and other substances like magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the formulation may also contain buffering agents. They may also be so formulated that they release the active ingredient(s) only or preferentially in a certain part of the intestinal tract, optionally in a delayed manner. The same may be achieved using embedded agents like, for example, polymeric substances and waxes.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. For such oral consumption it is desirable to combine the active ingredient with various sweetening or flavoring agents, coloring matter or dyes, if so desired. The diluents may be selected from water, ethanol, propylene glycol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, 1,3 butylene glycol, dimethyl formamide, oils for e.g. cottonseed, groundnut, corn, germ, olive, castor, sesame oils and the like, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and esters of fatty acids like sorbitan and various combination thereof. For mammals other than humans, the composition of the active substance are suitably modified.

For parenteral administration, the solutions of the compound is prepared in either sesame or peanut oil or in aqueous propylene glycol. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary, and the diluent should be first rendered isotonic.

The aqueous solutions are suitable for intravenous injection purposes while the oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The aforesaid compositions can be readily prepared under sterile conditions following well known standard pharmaceutical techniques by persons skilled in the art.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

For transdermal and topical administration, the dosage forms will include ointments, pastes, creams, lotions, gels, powders, solutions, sprays and inhalants. Transdermal patches may be prepared following standard drug delivery techniques and applied to the skin of a mammal, preferably a human or a dog, to be treated. Ophthalmic solutions, ear drops, eye ointments, powders can also be used as a medium of providing therapeutic dosages to the patients as will be necessary.

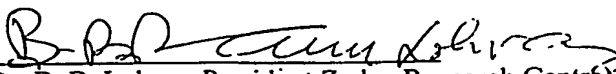
The ointments, pastes, creams and gels may, in addition to the active ingredient, contain excipients like animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, zinc oxide or their mixtures.

Powders and sprays may contain, in addition to the active substance, excipients like lactose, talc, silicic acid, aluminium hydroxide, calcium silicates and polyamide powder, or their mixtures. Sprays will additionally contain propellants like chlorofluorohydrocarbons.

The pharmaceutically acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro and against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically acceptable compounds of the present invention show activity against enterococci, pneumococci, and methicillin resistant strains of S.aureus and coagulase negative staphylococci, together with morganella strains. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by microbroth dilution technique as per NCCLS standards.

Dated this 5th 5th day of JUNE 2003

Signature


(Dr. B. B. Lohray, President Zydus Research Centre)
for Cadila Healthcare Ltd.

To
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